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ABSTRACTS OF ORIGINAL CONTRIBUTIONS

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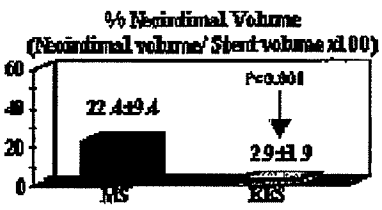

T139-61 **Is the Sirolimus Drug Eluting Stent Better Than Paclitaxel Coated Stent in "Real Life" Environment?**

Jean-Christophe E. Stauffer, Esq., Charles Seydoux, Esq., Jean-Jacques Goy, Esq., Clinic Cecil, Lausanne, Switzerland

Background: Active stents seems to improve the outcome after percutaneous intervention (PCI) in reducing MACE at 9 months. However no prospective data comparing various devices are available.
Method: Since March 2003, all patients suitable for stent implantation were randomized to receive either a sirolimus eluting stent (SES) or a paclitaxel active stent (PAS). Standard procedures were performed. Aspirin and clopidogrel were initiated for at least one year. Clinical outcome (MACE incidence at 9 months) is the primary end-point. Control angiography was performed only when clinically driven.
Results: A total of 102 pts were included (mean age 66±11), (24 female), received a 54 SES and 48 a PAS. Demographic data were comparable with a proportion of 8 pts with unstable angina. Diabetes was present in 7 pts the SES group and in 6 pts in the PAS group. Baseline data and follow-up at 3 months are presented in the table below.The incidence of MACE did not differ after a mean follow-up of 3 ±4 months between the 2 groups. Particularly no pt died in either group. MI did not occur either. Only sub-acute thrombosis was documented in 2 pts in the PAS group. TLR and TVR were required in 0 pts in the SES group versus 2 pts in the PAS group.
Conclusion: There was no significant difference in the incidence of MACE between sirolimus and paclitaxel group during this short follow-up. Nine-month follow-up will be available at time of presentation.

	LAD	CX	RCA	MACE
SES	21	12	21	2%
PAS	23	9	16	4%

T139-62 **Sirolimus Coated Stent Implantation Versus Intracoronary Beta-Irradiation for the Treatment of De Novo Lesions**

Christoph K. Naber, Karl Wegscheider, Katja Brauck, Holger Eggebrecht, Dietrich Baumgart, Axel Schmermund, Dirk Boese, Raimund Erbel, University Hospital, Essen, Germany, Institute for Statistics and Oeconometry, Hamburg, Germany

Introduction: Antiproliferative strategies for the reduction of restenosis such as vascular brachytherapy (VBT) and drug-eluting Stents have proven to be safe and highly effective. While VBT is effective for the treatment of in-stent restenosis, the data for the treatment of de-novo lesions are less convincing. This study aimed to compare the safety and efficacy of VBT and Sirolimus-eluting Stents (Cypher) for the treatment of de-novo lesions.
Methods: 53 individuals with de-novo lesions were treated with PTCA and Cypher-Stent implantation. Matching was performed with the cohort of patients with de-novo lesions from the European RENO registry. This registry included the first 1096 patients treated with intracoronary beta-irradiation (Sr90) in Europe. 123 patients met the matching criteria. Angiographic results and MACE rates (death, MI, TVR, TLR) were compared after 6 months.
Results: There were more diabetics in the Cypher-Stent group (32.1 vs. 19.5%; p=0.07) and more patients with multivessel disease (83.0 vs. 56.1%; p<0.001). Lesion length (13.3±4.1 vs. 13.2±3.9 mm) and reference diameter (3.1±0.5 vs. 3.0±0.5 mm) were comparable. Mean radiation dose in the RENO patients was 19.2±3.1 Gy, geographic miss occurred in 6.5%. New Stents were implanted in 94 RENO patients (76.4%).
After 6 months the overall MACE (21.1% vs. 7.5%; p=0.03) and binary restenosis rates (30.7 vs. 11.8; p=0.01) were significantly higher in the RENO group when compared with the Cypher patients. This was irrespective whether a new-stent was implanted or not.
Conclusion: the use of vascular brachytherapy for the treatment of de-novo lesions cannot be recommended. In those cases, the implantation of drug-eluting stents is clearly favourable.

ORAL CONTRIBUTIONS

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Drug-Eluting Stents: Randomized Trials

Tuesday, March 09, 2004, 2:00 p.m.-3:30 p.m.
Morial Convention Center, La Nouvelle C

2:00 p.m.

843-1 **REDOX Trial - Reduced Sirolimus Doses on the Bx VELOCITY™ Stent Four-Month Results**

J. Eduardo Sousa, Alexandre Abizaid, Feuzo Feres, Luiz A. Mattos, Luiz F. Tanajura, Amanda G.M.R. Sousa, Jeffrey Popma, Peter Fitzgerald, Joseph-Anthony Giorgianni, Roxanne A. Rodney, Instituto Dante Pazzanese de Cardiologia, Sao Paolo, Brazil

Background: The Cypher™ Sirolimus-eluting Coronary Stent has demonstrated a significant reduction in late loss and restenosis in four randomized trials. The next generation of drug-eluting stents are being developed with new materials which have potentially less surface area. For this reason there is a need to understand the effect of reducing the amount of drug on the stent. A trial was conducted to assess the safety and efficacy of two reduced sirolimus doses on the Bx VELOCITY™ stent, in patients with *de novo* native coronary artery lesions.
Method: A double blind, randomized study of the sirolimus-eluting Bx VELOCITY™ stent containing 45% or 70% of the current sirolimus dose (140 mcg/cm^2) was conducted in 60 patients (40 non-diabetic/20 diabetic) with *de novo* native coronary artery lesions ≤ 18mm in length and in vessels ≥3.0mm to ≤3.5mm in diameter. Four month angio and IVUS were performed.
Results: The 4-month follow-up TVF, TLR and MACE rates were zero for both groups. The table is a comparison of the angiographic results from the FIM and REDOX trials.

Angiographic - 4 Month Follow-up

	FIM – Slow Release	45% Sirolimus Dose	70% Sirolimus Dose
In-stent MLD, mm	2.85±0.46	2.74±0.39	2.65±0.48
In-stent DS, %	5.0±8.7	3.3±8.0	7.7±13.5
In-stent late loss, mm	0.09±0.25	0.10±0.31	0.10±0.35
In-stent binary restenosis, %	0.0	0.0	3.6 (1)

Conclusion: The results of the two reduced doses of sirolimus on the Bx VELOCITY™ stent are the same and are similar to those of the Cypher stent used in the FIM trial. These data suggest efficacy is maintained when reducing the total sirolimus dose on the Bx VELOCITY™.

2:15 p.m.

843-2 **Everolimus-Eluting Stents for the Prevention of Restenosis: Results of the FUTURE II Trial**

Eberhard Grube, Ricardo A. Costa, Roxana Mehran, Manuela Negoita, Yaal Glutz, Yoshihiro Tsuchiya, Martin Fahy, Ecaterina Cristea, Bahram Sahid, Horia Margineau, Ralf Muller, Georg Techen, Michael Rinck, Alexandra J. Lansky, Karl Eugen Hauptmann, Hans Storger, Cardiovascular Research Foundation, New York, NY, Heart Center, Siegburg, Germany

In the first-in-man experience, the everolimus-eluting stent (EES) demonstrated safety, feasibility and effectiveness to inhibit neointimal proliferation in human coronary arteries. The FUTURE II trial is a larger, prospective, randomized, blinded multicenter study of the EES (with a bioabsorbable polymer coating) vs. metallic stent (MS). We report the 6-month clinical and angiographic results.
Methods and Results: 64 patients (65 lesions) were randomized in a 1:2 ratio to EES (n=21) vs. MS (n=43). Baseline clinical and angiographic characteristics were similar in both groups, with 26.6% diabetics, mean vessel size of 2.95±0.48mm and lesion length of 11.43±3.44mm. Final and 6-month angiographic and clinical results are shown in the Table. **Conclusions:** The expanded FUTURE II trial confirmed the efficacy demonstrated in the FUTURE I trial with a significant 85.9% reduction in neointimal proliferation (in-stent late loss) with EES compared to the bare metal stent. There was no exaggerated hyperplasia at the proximal and/or distal edges of the stent in the everolimus group.

Tuesday, March 09, 2004, 2:00 p.m.-3:30 p.m.
Morial Convention Center, La Nouvelle C

2:00 p.m.

843-1 **REDOX Trial - Reduced Sirolimus Doses on the Bx VELOCITY™ Stent Four-Month Results**

J. Eduardo Sousa, Alexandre Abizaid, Fausto Feres, Luiz A. Mattos, Luiz F. Tanajura, Amanda G.M.R. Sousa, Jeffrey Popma, Peter Fitzgerald, Joseph-Anthony Giorgianni, Roxanne A. Rodney, Instituto Dante Pazzanese de Cardiologia, Sao Paolo, Brazil

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Method: A double blind, randomized study of the sirolimus-eluting Bx VELOCITY™ stent containing 45% or 70% of the current sirolimus dose (140 mcg/cm^2) was conducted in 60 patients (40 non-diabetic/20 diabetic) with *de novo* native coronary artery lesions ≤ 18mm in length and in vessels ≥3.0mm to ≤3.5mm in diameter. Four month angio and IVUS were performed.

Results: The 4-month follow-up TVF, TLR and MACE rates were zero for both groups. The table is a comparison of the angiographic results from the FIM and REDOX trials.

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2:15 p.m.

843-2 **Everolimus-Eluting Stents for the Prevention of**

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VOLUME 346 JUNE 6, 2002 NUMBER 23

A RANDOMIZED COMPARISON OF A SIROLIMUS-ELUTING STENT WITH A STANDARD STENT FOR CORONARY REVASCULARIZATION

MARIE-CLAUDE MORICE, M.D., PATRICK W. SERRUYS, M.D., PH.D., J. EDUARDO SOUSA, M.D., JEAN FAJADET, M.D., ERNESTO BAN HAYASHI, M.D., MARCO PERIN, M.D., ANTONIO COLOMBO, M.D., G. SCHULER, M.D., PAUL BARRAGAN, M.D., GIULIO GUAGLIUMI, M.D., FERENC MOLNÀR, M.D., AND ROBERT FALOTICO, PH.D., FOR THE RAVEL STUDY GROUP*

ABSTRACT

Background The need for repeated treatment of restenosis of a treated vessel remains the main limitation of percutaneous coronary revascularization. Because sirolimus (rapamycin) inhibits the proliferation of lymphocytes and smooth-muscle cells, we compared a sirolimus-eluting stent with a standard uncoated stent in patients with angina pectoris.

Methods We performed a randomized, double-blind trial to compare the two types of stents for revascularization of single, primary lesions in native coronary arteries. The trial included 238 patients at 19 medical centers. The primary end point was in-stent late luminal loss (the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months). Secondary end points included the percentage of in-stent stenosis of the luminal diameter and the rate of restenosis (luminal narrowing of 50 percent or more). We also analyzed a composite clinical end point consisting of death, myocardial infarction, and percutaneous or surgical revascularization at 1, 6, and 12 months.

Results At six months, the degree of neointimal proliferation, manifested as the mean (±SD) late luminal loss, was significantly lower in the sirolimus-stent group (−0.01±0.33 mm) than in the standard-stent group (0.80±0.53 mm, $P<0.001$). None of the patients in the sirolimus-stent group, as compared with 26.6 percent of those in the standard-stent group, had restenosis of 50 percent or more of the luminal diameter ($P<0.001$). There were no episodes of stent thrombosis. During a follow-up period of up to one year, the overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group ($P<0.001$). The difference was due entirely to a higher rate of revascularization of the target vessel in the standard-stent group.

Conclusions As compared with a standard coronary stent, a sirolimus-eluting stent shows considerable promise for the prevention of neointimal proliferation, restenosis, and associated clinical events. (N Engl J Med 2002;346:1773-80.)

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THE growing use of stents has improved the results of percutaneous coronary revascularization.[1-5] However, in-stent restenosis continues to limit the long-term success of this approach.[6,7] For example, in a recent randomized comparison of coronary-artery bypass surgery and stenting in patients with multivessel disease, additional revascularization procedures were performed within one year in 21.0 percent of patients who had undergone stenting, as compared with 3.8 percent of patients treated surgically.[8]

In controlled trials, several pharmaceutical agents have failed to inhibit restenosis after coronary interventions.[9] In contrast, the systemic and local delivery of sirolimus (rapamycin), a macrocyclic lactone that inhibits cytokine-mediated and growth-factor–mediated proliferation of lymphocytes and smooth-muscle cells, reduced neointimal proliferation in studies in animals and in a small clinical study.[10-12] We conducted a study to compare the performance of a coronary stent that slowly releases sirolimus over a period of 30 days with that of a standard uncoated stent.

METHODS

Selection of Patients

The study was a randomized, double-blind trial performed at 19 medical centers (listed in the Appendix). It was approved by

From Institut Cardiovasculaire Paris Sud, Massy, France (M.-C.M.); Thoraxcentrum, Rotterdam, the Netherlands (P.W.S.); Institute Dante Pazzanese de Cardiologia, São Paulo, Brazil (J.E.S.); Clinique Pasteur, Toulouse, France (J.F.); Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico (E.B.H.); the Heart Institute of the University of São Paulo, São Paulo, Brazil (M.P.); Centro Cuore Columbus, Milan, Italy (A.C.); Herzzentrum, Leipzig, Germany (G.S.); Centre Hospitalier Privé Beauregard, Marseilles, France (P.B.); Azienda Ospedaliera Ospedali Riuniti di Bergamo, Bergamo, Italy (G.G.); Semmelweis Egyetem Egészségtudomanyi Kar, Budapest, Hungary (F.M.); and Cordis, Johnson & Johnson, Warren, N.J. (R.F.). Address reprint requests to Dr. Morice at the Institut Hospitalier Jacques Cartier, Ave. du Noyer Lambert, 91300 Massy, France.

*The members of the RAVEL (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) study group are listed in the Appendix.

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the ethics committee at each participating institution, and all patients gave written informed consent. The study was conducted from August 2000 to August 2001.

Patients were eligible for the study if they were 18 to 85 years old, were not pregnant and were protected against pregnancy during the study, and had received a diagnosis of stable or unstable angina or silent ischemia. Additional eligibility criteria were the presence of a single primary target lesion in a native coronary artery that was 2.5 to 3.5 mm in diameter and that could be covered by an 18-mm stent; stenosis of 51 to 99 percent of the luminal diameter, as estimated visually; and a flow rate of grade 1 or higher according to the classification of the Thrombolysis in Myocardial Infarction (TIMI) trial. Patients were not eligible for enrollment if they had an evolving myocardial infarction, stenosis of the left-main coronary artery, unprotected by a graft, that caused luminal narrowing of 50 percent or more, an ostial lesion, a calcified lesion that could not be completely dilated before stenting, an angiographically visible thrombus within the target lesion, a left ventricular ejection fraction of less than 30 percent, or an intolerance of aspirin, clopidogrel, ticlopidine, heparin, stainless steel, or contrast material.

The Sirolimus-Eluting Stent

Sirolimus was blended in a mixture of nonerodable polymers, and a layer of sirolimus–polymer matrix with a thickness of 5 μm was applied to the surface of a stainless-steel, balloon-expandable stent (Bx Velocity, Cordis, Johnson & Johnson). The stent was loaded with a fixed amount of sirolimus per unit of metal surface area (140 μg of sirolimus per square centimeter). A layer of drug-free polymer was applied on top of the drug–polymer matrix as a diffusion barrier to prolong the release of the drug. The stent was designed to release approximately 80 percent of the drug within 30 days after implantation.

Study Procedures

Codes for random assignments to the treatment groups were generated by computer in blocks of four and were distributed in sealed envelopes to each participating center. Patients were randomly assigned to the groups in a 1:1 ratio.

Lesions were treated with the use of standard interventional techniques. Stenting without predilation was prohibited. After successful predilation, patients were randomly assigned in a double-blind fashion to receive a standard uncoated stent or a sirolimus-eluting stent mounted on a rapid-exchange delivery system and inflated to 10 to 16 atm. The sirolimus-eluting stents were indistinguishable, except under a microscope, from the uncoated stents. After the stent had been implanted, further dilation was performed as necessary to ensure that there was less than 20 percent residual stenosis, with a TIMI grade III flow rate. In case of dissection or incomplete coverage of the lesion, additional stents of the same type as the assigned stent (coated or uncoated) were used.

Intravenous boluses of heparin were administered to maintain an activated clotting time that exceeded 250 seconds during the procedure and were discontinued within 12 hours. Treatment with aspirin, at a dose of at least 100 mg per day, was begun 12 hours before the procedure and continued indefinitely. A loading dose of 300 mg of clopidogrel was administered 48 hours before the procedure, followed by 75 mg daily for eight weeks. Alternatively, treatment with ticlopidine, at a dose of 250 mg twice daily, was begun one day before the procedure and continued for eight weeks. A successful procedure was defined as the successful implantation of the study device, with stenosis of less than 20 percent of the vessel diameter and no major cardiac events during the hospital stay.

Follow-up

Patients were evaluated at 30 days and at 6 and 12 months. They were asked specific questions about the interim development of angina, according to the Canadian Cardiovascular Society classification of stable angina[13] and the Braunwald classification of unstable angina.[14] The patients were also monitored for major cardiac events and for the need for additional revascularization of the index target lesion. An electrocardiogram was obtained at each visit, and an angiographic study was performed at a mean (±SD) of 180±30 days. Other studies and tests were performed at the discretion of the investigators at the participating centers. Because of the double-blind nature of the study, the decision to perform further revascularization of the target lesion or vessel after the six-month angiographic study was also left to the investigators' discretion.

Quantitative Coronary Angiographic Evaluation

Coronary angiograms were obtained in multiple views after the intracoronary injection of nitrates. Quantitative analyses of all angiographic data before, during, and after the procedure were performed by an independent core laboratory (Cardialysis, Rotterdam, the Netherlands) with the use of edge-detection techniques. The luminal diameter of the coronary artery and the degree of stenosis were measured before dilation, at the end of the procedure, and at six months. Restenosis was defined as stenosis of 50 percent or more of the luminal diameter. Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the procedure and the diameter at six months. The target lesion was defined as the stented segment plus the 5-mm segments proximal and distal to the stented segment.

Intravascular Ultrasound Substudy

At the six-month visit, intravascular ultrasound examinations were performed by six centers in subgroups of 48 patients who had received a sirolimus-eluting stent and 47 who had received an uncoated stent.

Study End Points

The primary angiographic end point was in-stent luminal late loss, as determined by quantitative angiography. Secondary end points included the percentage of in-stent stenosis of the luminal diameter, the rate of restenosis (luminal narrowing of 50 percent or more), and the minimal luminal diameter of the stented segment and of the 5-mm segments proximal and distal to the stent at six months.

The primary clinical end point of the study was a composite of major cardiac events, including death, Q-wave or non–Q-wave myocardial infarction, coronary-artery bypass grafting, and revascularization of the target lesion or vessel 30 days, 6 months, and 12 months after the index procedure. A non–Q-wave myocardial infarction was defined by an increase in the creatine kinase level to more than twice the upper limit of the normal range, accompanied by an increased level of creatine kinase MB, in the absence of new Q waves on the surface electrocardiogram.

The end points were adjudicated by an independent clinical-events committee. In addition, a data and safety monitoring board that was not affiliated with the study sponsor reviewed the data to identify any safety issues related to the conduct of the study.

Statistical Analysis

We calculated that with a sample of 207 patients, the study would have 90 percent power to detect a difference in the mean late luminal loss of 0.25 mm between the two groups, assuming a standard deviation of 0.55 mm in each group, with the use of a two-group t-test and a two-sided significance level of 0.05.

All analyses were based on the intention-to-treat principle. For continuous variables, differences between the treatment groups were evaluated by analysis of variance or Wilcoxon's rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analyzed with Fisher's exact test.

Revascularization of the target lesion or vessel and the composite of major adverse events during follow-up were analyzed by the

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Kaplan–Meier method. Differences between the event-free survival curves for the two groups were compared with the use of the Wilcoxon and log-rank tests.

All listed authors participated in the study design, enrollment of patients, and data interpretation. The data were held by the core laboratory (Cardialysis, Rotterdam, the Netherlands), but all investigators had full access to them.

RESULTS

Characteristics of the Patients

Between August 2000 and January 2001, 120 patients were randomly assigned to receive the sirolimus-eluting stent, and 118 were assigned to receive the standard stent. With the exception of a significantly higher percentage of men in the standard-stent group, the two groups were similar with respect to all variables examined (Table 1). Overall, 76 percent of the patients were men, and the mean age was 60.7 years, with the expected prevalences of dyslipidemia, diabetes, hypertension, and current tobacco use. Stenting was performed because of unstable angina in 50 percent of the patients. The target vessel was the left anterior descending coronary artery in 50 percent of the patients, the right coronary vessel in 27 percent, and the left circumflex artery in 23 percent. Nearly all the treated lesions were class B1 or B2 according to the American College of Cardiology–American Heart Association classification. Although all the target index lesions were primary lesions, 1.7 percent of the patients had undergone previous coronary-artery surgery and 18.1 percent had undergone previous percutaneous interventions for the treatment of other lesions.

Procedural Characteristics

The lesions in the two groups were treated similarly with the use of conventional techniques. Platelet glycoprotein IIb/IIIa inhibitors, the use of which was left to the discretion of the investigators at the participating centers, were administered to 10.1 percent of the patients in the sirolimus-stent group and 9.5 percent of those in the standard-stent group. The two groups did not differ significantly with respect to the

TABLE 1. BASE-LINE CHARACTERISTICS OF THE OVERALL PATIENT POPULATION AND OF EACH TREATMENT GROUP.*

CHARACTERISTIC	ALL PATIENTS (N=238)	SIROLIMUS STENT (N=120)	STANDARD STENT (N=118)
Age (yr)	60.7±10.4	61.8±10.7	59.7±10.1
Male sex (%)	76	70	81
Previous myocardial infarction (%)	36	38	34
Diabetes mellitus (%)	19	16	21
Treated hypercholesterolemia (%)	40	38	43
Treated hypertension (%)	61	62	61
Current smoker (%)	30	27	33
Angina pectoris (%)†			
Unstable	50	48	52
Stable	39	41	37
Silent ischemia (%)	11	11	11
Target coronary artery (%)‡			
LAD	50	49	51
RCA	27	27	27
LCX	23	24	22
Lesion type (%)§			
A	6	8	4
B1	37	38	35
B2	57	54	61
Reference diameter of the vessel (mm)	2.62±0.53	2.60±0.54	2.64±0.52
Length of lesion (mm)	9.58±3.25	9.56±3.33	9.61±3.18

*Plus–minus values are means ±SD. There were no significant differences between the treatment groups except for male sex (P=0.05).

†Unstable angina was defined according to the Braunwald classification,[14] and stable angina according to the classification of the Canadian Cardiovascular Society.[15]

‡LAD denotes left anterior descending coronary artery, RCA right coronary artery, and LCX left circumflex artery.

§The classification of the American College of Cardiology–American Heart Association was used.

rate of successful stent placement (96.6 percent in the sirolimus-stent group and 93.1 percent in the standard-stent group).

Quantitative Angiographic Analysis

Angiographic data at six months were available for 211 of the 238 patients (88.7 percent). The mean reference diameter of the target vessel and the mean length of the lesion at base line were similar in the two groups (Table 1). The mean minimal luminal diameter of the stented segment and the length of the lesion before and after the procedure, as well as the reduction in stenosis immediately after the procedure, were also similar in the two groups (Table 2). At six months, however, the mean minimal luminal diameter of the stented segment was significantly greater in the sirolimus-stent group. The mean in-stent late loss, percentage of stenosis, and percentage of patients with 50 percent or more stenosis were −0.01 mm, 14.7 percent, and 0 percent, respectively, in the sirolimus-stent group, as compared with 0.80 mm, 36.7 percent, and 26.6 percent, respectively, in the standard-stent group ($P<0.001$ for each comparison). Figure 1 shows the cumulative frequency of stenosis immediately after the index procedure and at six months in each treatment group. Table 2 shows the results of subsegmental quantitative angiographic analyses. The late luminal loss at both the proximal and the distal edges of the stent was significantly less in the sirolimus-stent group than in the standard-stent group ($P<0.001$ for both comparisons). There was a small degree of restenosis at the edges of the standard stent that was not present with the sirolimus-eluting stent.

In the subgroup of patients with diabetes, 19 patients received sirolimus-eluting stents, and 25 received standard stents. The minimal luminal diameter before and after stenting was similar in the two groups (0.99 mm in the sirolimus-stent group and 0.93 mm in the standard-stent group before the procedure and 2.37 and 2.36 mm, respectively, afterward). However, at six months, the minimal luminal diameter was markedly larger in the sirolimus-stent group (2.29 mm, vs. 1.56 mm in the standard-stent group; $P<0.001$); consequently, the late loss was smaller (0.07 mm in the sirolimus-stent group vs. 0.82 mm in the standard-stent group, $P<0.001$) and the restenosis rate was lower (0 percent vs. 41.7 percent, $P=0.002$).

Intravascular Ultrasound Evaluation

At six months, intravascular ultrasound examination showed no significant differences between the two groups with respect to the volume of the stent, the volume of the overall vessel, or the volume of the plaque behind the stent. However, the sirolimus-stent group had significantly less neointimal hyperplasia than did the standard-stent group (2±5 vs. 37±28 mm^3) and significantly less volume obstruction, defined as the ratio of the volume of hyperplasia to the volume of the stent, multiplied by 100 (1±3 percent vs. 29±20 percent) ($P<0.001$ for both comparisons). These findings are consistent with the

TABLE 2. RESULTS OF SUBSEGMENTAL QUANTITATIVE ANGIOGRAPHIC ANALYSIS.*

VARIABLE	PROXIMAL EDGE			STENTED SEGMENT			DISTAL EDGE		
	SIROLIMUS STENT	STANDARD STENT	P VALUE	SIROLIMUS STENT	STANDARD STENT	P VALUE	SIROLIMUS STENT	STANDARD STENT	P VALUE
Mean diameter (mm)									
Before procedure	2.66±0.59	2.62±0.58		—	—		2.33±0.55	2.41±0.58	
After procedure	2.78±0.55	2.78±0.53		2.83±0.41	2.82±0.40		2.45±0.47	2.50±0.52	
At 6 mo	2.73±0.59	2.55±0.60	<0.05	2.88±0.48	2.23±0.50	<0.001	2.50±0.53	2.43±0.52	
Minimal luminal diameter (mm)									
Before procedure	2.27±0.60	2.23±0.66		0.94±0.31	0.95±0.35		1.97±0.54	2.07±0.59	
After procedure	2.47±0.53	2.46±0.54		2.43±0.41	2.41±0.40		2.13±0.47	2.21±0.51	
At 6 mo	2.41±0.58	2.19±0.64	0.01	2.42±0.49	1.64±0.59	<0.001	2.20±0.51	2.12±0.51	
Stenosis (% of luminal diameter)									
Before procedure	15.2±9.1	16.2±12.2		63.6±10.7	64.0±10.2		15.9±9.4	14.6±9.8	
After procedure	11.4±5.0	12.1±5.2		11.9±5.9	14.0±6.8	<0.05	13.0±5.2	11.7±5.1	0.057
At 6 mo	12.2±4.7	15.4±8.4	<0.001	14.7±7.0	36.7±18.1	<0.01	12.2±4.9	13.2±6.9	
Late loss (mm)†	0.05±0.39	0.29±0.48	<0.001	−0.01±0.33	0.80±0.53	<0.001	−0.09±0.30	0.12±0.44	<0.001
≥50% restenosis (% of patients)	0	0		0	26.6	<0.001	0	0	

*Plus–minus values are means ±SD.

†Late loss was defined as the difference between the minimal luminal diameter immediately after placement of the stent and the minimal luminal diameter at six months. The data are for patients for whom both post-procedural and follow-up measurements of the minimal luminal diameter were available.

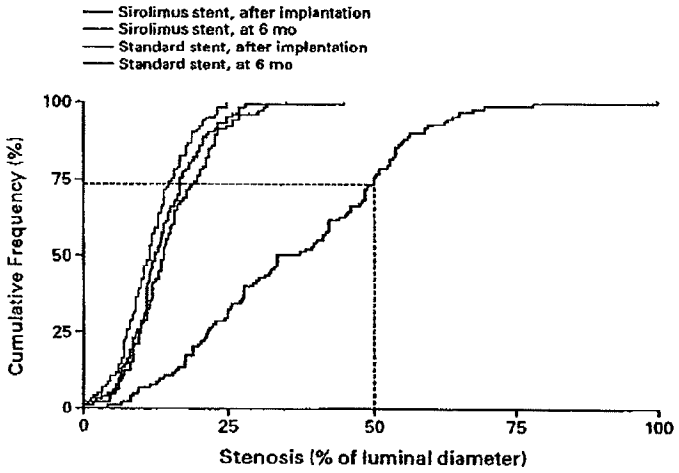

Figure 1. Cumulative Frequency of Stenosis Immediately after Stenting and at Six Months in Patients Who Received Sirolimus-Eluting Stents and in Those Who Received Standard Stents.
The broken lines indicate the percentage of lesions with restenosis (above the line, 22.9 percent) and without restenosis (below the line, 77.1 percent) according to the study definition.

nearly complete suppression of in-stent neointimal hyperplasia by sirolimus. In addition, there was no evidence of an "edge effect," aneurysm formation, in-stent thrombosis, or persistent dissection.

Adverse Events

Major cardiac events are listed in Table 3. Three patients in each group had a myocardial infarction at the time of stenting. In the sirolimus-stent group, two of the patients with myocardial infarction underwent angiography in the hospital, which showed a patent stent in each. The third patient had a non–Q-wave myocardial infarction, and the angiographic study performed at six months showed a patent stent. One recipient of a standard stent underwent further percutaneous revascularization of the target vessel for the treatment of a lesion other than the index lesion.

During a follow-up period of up to one year, two patients in the standard-stent group (1.7 percent) died: one had a myocardial infarction and died suddenly several weeks later, and the other had a gastric hemorrhage. Two patients in the sirolimus-stent group (1.7 percent) also died: one had a subarachnoid hemorrhage, and the other had gastrointestinal cancer. One patient in each group underwent surgical revascularization of the index target vessel.

Percutaneous revascularization of the target lesion was performed in 27 recipients of standard stents (22.9 percent) but in none of the recipients of sirolimus-eluting stents ($P=0.001$). Subacute or late thrombotic occlusion of the stent did not occur in either group.

Kaplan–Meier estimates of event-free survival are shown in Figure 2. The overall rate of major cardiac events was 5.8 percent in the sirolimus-stent group and 28.8 percent in the standard-stent group ($P<0.001$). The difference between the two groups was entirely due to the greater need for repeated revascularization of the target vessel in the standard-stent group. No adverse effects were attributable to the sirolimus coating of stents.

DISCUSSION

We found that use of a sirolimus-eluting stent resulted in the virtual elimination of in-stent neointimal hyperplasia; thus, there was no angiographic evidence of restenosis and no need for repeated interventions. Since the introduction of angioplasty, restenosis has been a major factor limiting the long-term success of percutaneous coronary revascularization.[15] The refinement of stenting techniques in the past decade has substantially improved the overall results of the procedure.[3,4,16,17] Despite considerable efforts to prevent the development of restenosis, however, including systemic or local delivery of biochemical substanc-

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TABLE 3. CARDIAC EVENTS IN THE HOSPITAL AND DURING ONE YEAR OF FOLLOW-UP.

EVENT	SIROLIMUS STENT (N=120)	STANDARD STENT (N=118)
Before discharge		
Death — no.	0	0
Myocardial infarction — no.	3	3
Q-wave	2	1
Non–Q-wave	1	2
Coronary-artery bypass grafting — no.	0	0
After discharge		
Death — no.	2	2*
Myocardial infarction — no.	1	2
Q-wave	0	0
Non–Q-wave	1	2
Coronary-artery bypass grafting	1†	1
Percutaneous revascularization of target lesion — no.	0	27
Total — no. (%)	7 (5.8)	34 (28.8)‡
Cumulative event-free survival — %	94.1	70.9§

*Both patients had had previous myocardial infarctions.

†Coronary-artery bypass grafting was performed to treat progressive disease of the left main coronary artery and the ostium of the anterior descending coronary artery, not the target lesion.

‡P<0.001 for the comparison between the two groups with the use of Fisher's exact test.

§P<0.001 for the comparison between the two groups with the use of the log-rank test.

es and drugs[9] and the use of various devices,[18-22] additional target-vessel revascularization is required in more than 15 percent of patients.[8,23] Although catheter-based brachytherapy is effective in the treatment of in-stent restenosis,[24] its value in the treatment of primary lesions is less clear. Furthermore, the use of brachytherapy is limited by its high cost and burdensome instrumentation and by the risks inherent in the use of radioisotopes.

In this context, the benefit of the sirolimus-eluting stent in our study was particularly striking. This new device appears to have virtually eliminated the development of neointimal proliferation. Yet its use did not require special implantation techniques or instrumentation and was innocuous within the time frame of the study.

In the group of patients with sirolimus-eluting stents, the percentage of stenosis at six months was essentially the same as that immediately after the procedure and was in all cases less than 35 percent. The virtual absence of late loss in the luminal diameter in this group is consistent with the arrest of in-stent neointimal proliferation by sirolimus. Also noteworthy was the absence of restenosis and major cardiac events in the patients with diabetes who received sirolimus-eluting stents. Whether these effects can be sustained for several years remains to be determined. The results thus far suggest that the use of an appropriate therapeutic agent when growth-factor–induced cell proliferation is at its peak can have substantial effects on the process of in-stent restenosis.

Sirolimus, a macrolide antifungal agent with a

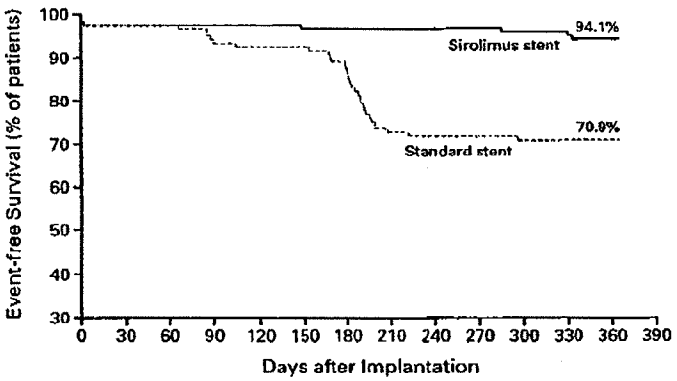

Figure 2. Kaplan–Meier Estimates of Survival Free of Myocardial Infarction and Repeated Revascularization among Patients Who Received Sirolimus-Eluting Stents and Those Who Received Standard Stents.

The rate of event-free survival was significantly higher in the sirolimus-stent group than in the standard-stent group (P<0.001 by the Wilcoxon and log-rank tests).

unique antiproliferative mode of action and powerful immunosuppressant properties, inhibits several regulators of cell-cycle progression and the migration of vascular smooth-muscle cells.[25] Yet studies in animals have shown that reendothelialization may occur even while sirolimus is being eluted.[26] Moreover, recent experiments in animals have shown that sirolimus blocks inflammation.[26] These antiproliferative, antimigratory, and antiinflammatory properties are responsible for the efficacy of sirolimus therapy in preventing acute rejection of renal allografts and arteriopathy of cardiac allografts, as well as in-stent restenosis. The wide safety margin of sirolimus[27] and the minuscule amounts of drug released into the blood explain the absence of detectable adverse effects in our trial and in a previous clinical study.[12]

The restenosis rate of 27 percent in the standard-stent group may seem high. However, on the basis of a linear regression model derived from the Stent Restenosis Study and the Benestent I and II studies (unpublished data), the predicted rate of restenosis for our patient cohort was approximately 28 percent. Of the 27 patients in the standard-stent group who underwent revascularization of the target vessel (22.9 percent), 16 did so because of angina or abnormal stress tests and 11 because of angiographic evidence of restenosis.

Despite the absence of late luminal loss in the sirolimus-stent group, reendothelialization presumably occurred, since none of the patients in the group had acute, subacute, or late thrombosis, even though they received combined antiplatelet therapy for only two months. These findings are similar to reported observations in animals.[26]

We enrolled patients with single lesions that were up to 18 mm long. Whether the positive results in these patients can be expected in patients with more complex or more extensive disease remains to be determined. However, a subgroup analysis showed that the results in patients with diabetes were similar to those in patients without diabetes.

In this trial, 2.5-mm stents were used in 18 percent of the patients randomly assigned to the sirolimus-stent group. Furthermore, division of the treatment groups into thirds according to the vessel diameter revealed virtually identical late luminal loss, even in the smallest arteries.

Stents that deliver drugs are complex devices with three components: the stent, the drug, and the coating. The long-term outcome of treatment with these devices will depend on the response to all three components.

In conclusion, patients with angina who received sirolimus-eluting stents for the treatment of single, primary lesions in native coronary arteries had no angiographic evidence of late luminal loss or in-stent restenosis at six months, no episodes of thrombosis, and a very low rate of cardiac events at one year.

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APPENDIX

The following investigators and institutions participated in the RAVEL study: **Steering Committee** — M.C. Morice (chairperson), Massy, France; P.W. Serruys (cochairperson), Rotterdam, the Netherlands; K. Nijssen, Rotterdam, the Netherlands; C. Bode, Freiburg, Germany; P. Barragan, Marseilles, France; and M. Delattre, Waterloo, Belgium; **Sponsor** — Cordis, Johnson & Johnson, Warren, N.J., E. Wülfert (program coordinator) and C. Demeyere, Waterloo, Belgium; **Data and Safety Monitoring Board** — J.G.P. Tijssen, Amsterdam; G. Steg, Paris; and P. Vranckx, Rotterdam, the Netherlands; **Data Management** — Cardialysis, Rotterdam, the Netherlands; **Clinical Events Committee** — J. Deckers (chairperson), Rotterdam, the Netherlands; J.A.M. te Riele, Breda, the Netherlands; and L.G.P.M. van Zeijl, Rotterdam, the Netherlands; **Core Angiographic Laboratory** — C. Disco, K. Nijssen, and A. Spierings, Cardialysis, Rotterdam, the Netherlands; **Clinical sites** — M.C. Morice, T. Lefèvre, and Y. Louvard, Institut Cardiovasculaire Paris Sud, Massy, France; P.W. Serruys, M. van den Brand, D. Foley, W. van der Giessen, P. de Feyter, P. Smits, and J. Vos, Thoraxcentrum, Rotterdam, the Netherlands; C. Bode, M. Rave, and C. Holubarsch, Albert Ludwigs Universitätskliniken, Freiburg, Germany; P. Barragan, J.B. Simeoni, C.O. Roquebert, and P. Commeau, Clinique Beauregard, Marseilles, France; G. Schuler, P. Sick, and M. Woinke, Herzzentrum, Leipzig, Germany; G.J. Laarman and F. Kiemeney, Onze Lieve Vrouwe Gasthuis, Amsterdam; W. Wijns, B. de Bruyne, J. Bartunek, P. de Bruyne, G.R. Heyndrickx, Onze Lieve Vrouwe Kliniek, Aalst, Belgium; J. Fajadet, J. Marco, B. Farah, P. Sousa, and M. Boccalatte, Clinique Pasteur, Toulouse, France; J.L. Guermonprez, Hôpital Européen Georges Pompidou, Paris; A. Colombo, C. di Mario, R. Albiero, and N. Corvaja, Centro Cuore Columbus, Milan, Italy; A. Bartorelli, S. Galli, F. Fabbiochi, P. Motorsi, D. Trabattoni, and A. Loaldi, Centro Cardiologico Monzino, Milan, Italy; G. Guagliumi, O. Valsecchi, M. Tespili, A. Vassileva, and A. Saimo, Ospedali Riuniti di Bergamo, Bergamo, Italy; F. Molnár, R.G. Kiss, L. Major, and G. Bokori, Semmelweis Egyetem Egészégtudomanyi Kar, Budapest, Hungary; E. Ban Hayashi, I. Sanchez, J. Gaspar, R. Villavicencio, and M.A. Pena Duque, Instituto Nacional de Cardiologia, Mexico City, Mexico; J.E. Sousa, E. Sousa, A.S. Abizaid, A. Abizaid, A. Sousa, R. Feres, L.A. Mattos, M. Costa, and R. Staico, Institute Dante Pazzanese de Cardiologia, São Paulo, Brazil; M. Perin, E. Ribeiro, E. Martinez, P. Soares, and F. Demartino, University Hospital of São Paulo, São Paulo, Brazil; D. Blanchard and O. Bar, Clinique Saint-Gatien, Tours, France; A. Cribier, H. Eltchaninoff, Centre Hospitalier Universitaire de Rouen, Rouen, France.

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Sirolimus-Eluting Stents versus Standard Stents in Patients with Stenosis in a Native Coronary Artery

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ABSTRACT

BACKGROUND

Preliminary reports of studies involving simple coronary lesions indicate that a sirolimus-eluting stent significantly reduces the risk of restenosis after percutaneous coronary revascularization.

METHODS

We conducted a randomized, double-blind trial comparing a sirolimus-eluting stent with a standard stent in 1058 patients at 53 centers in the United States who had a newly diagnosed lesion in a native coronary artery. The coronary disease in these patients was complex because of the frequent presence of diabetes (in 26 percent of patients), the high percentage of patients with longer lesions (mean, 14.4 mm), and small vessels (mean, 2.80 mm). The primary end point was failure of the target vessel (a composite of death from cardiac causes, myocardial infarction, and repeated percutaneous or surgical revascularization of the target vessel) within 270 days.

RESULTS

The rate of failure of the target vessel was reduced from 21.0 percent with a standard stent to 8.6 percent with a sirolimus-eluting stent ($P<0.001$) — a reduction that was driven largely by a decrease in the frequency of the need for revascularization of the target lesion (16.6 percent in the standard-stent group vs. 4.1 percent in the sirolimus-stent group, $P<0.001$). The frequency of neointimal hyperplasia within the stent was also decreased in the group that received sirolimus-eluting stents, as assessed by both angiography and intravascular ultrasonography. Subgroup analyses revealed a reduction in the rates of angiographic restenosis and target-lesion revascularization in all subgroups examined.

CONCLUSIONS

In this randomized clinical trial involving patients with complex coronary lesions, the use of a sirolimus-eluting stent had a consistent treatment effect, reducing the rates of restenosis and associated clinical events in all subgroups analyzed.

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*The SIRIUS investigators are listed in the Appendix.

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THE DEMONSTRATED CLINICAL USEfulness of the implantation of a coronary stent as the preferred method of percutaneous revascularization is due to improved procedural safety as compared with balloon angioplasty and reduced rates of restenosis.[1-7] But despite the use of coronary stents, the frequency of restenosis may be more than 30 percent in several subgroups of patients, including subgroups with diabetes mellitus, small coronary vessels, and long lesions.[8-15]

During the past two decades, attempts to reduce restenosis after angioplasty with the use of locally delivered or systemic pharmaceutical agents have been largely unsuccessful.[16-19] Recently, sirolimus (rapamycin), a cytostatic macrocyclic lactone with both antiinflammatory and antiproliferative properties,[20-22] delivered from a polymer-encapsulated stent was shown in small registry studies and randomized clinical trials to reduce the risk of restenosis in patients who were at low risk for restenosis.[23-25] We conducted a study to determine the clinical usefulness of the sirolimus-eluting stent in patients with more challenging coronary stenoses.

METHODS

STUDY DESIGN AND ELIGIBILITY

This randomized, double-blind study complied with the provisions of the Declaration of Helsinki regarding investigation in humans and was approved by the Food and Drug Administration. The study was approved by the institutional review boards at all 53 investigational sites, and written informed consent was obtained from all patients.

Eligible patients had a history of stable or unstable angina and signs of myocardial ischemia. A single newly diagnosed target lesion in a native coronary artery resulting in stenosis of 51 to 99 percent of the luminal diameter and measuring 15 to 30 mm in length (as estimated visually on angiography) was treated. Major criteria for exclusion were recent myocardial infarction (within the previous 48 hours); an ejection fraction of less than 25 percent; a target lesion in an ostium, a bifurcation, or an "unprotected" left main coronary artery or in a vessel with thrombus or severe calcification; and treatment of nontarget lesions in the same or a different coronary vessel during the index procedure.

Before the index procedure, an automated telephone randomization system was used to randomly assign eligible patients in a double-blind manner to treatment with a sirolimus-eluting stent or a standard stent (Bx Velocity, Cordis) in a 1:1 ratio at each site. Randomization blocks were created and were stratified according to the clinical center and the presence or absence of diabetes mellitus.

CORONARY-STENT PROCEDURE

Before and after the index procedure, all patients received oral aspirin (325 mg daily) and oral clopidogrel (a loading dose of 300 to 375 mg 24 hours before the procedure and then 75 mg daily for three months). During the procedure, intravenous heparin boluses were administered. The use of intravenous glycoprotein IIb/IIIa inhibitors was at the discretion of the physician. Lesions were treated with the use of standard interventional techniques, including mandated balloon dilation before the placement of the stent. One or two stents of the assigned type were used to treat the target lesion. The sirolimus-eluting stents and the standard stents (available in lengths of 8 mm and 18 mm and in diameters of 2.5 mm, 3.0 mm, and 3.5 mm) were identical in appearance. The sirolimus-eluting stents contained 140 μg of sirolimus per square centimeter of stent-surface area within a copolymer matrix that was 5 to 10 μm thick and was designed to release approximately 80 percent of the total dose of sirolimus in 30 days. Both the physician and the patient were unaware of the treatment-group assignment.

DATA COLLECTION, FOLLOW-UP, AND CORE LABORATORY ANALYSES

All data were submitted to a data coordinating center (the Cardiovascular Data Analysis Center, Harvard Clinical Research Institute, Harvard Medical School, Boston), and the investigators had full access to the data. The investigators also initiated, performed, and reviewed all analyses and made the decisions about publication. Clinical follow-up information was obtained for all patients by the research coordinators at each site at 30, 90, 180, and 270 days. All clinical end points were adjudicated by an independent clinical-events committee that was unaware of the treatment-group assignments. A separate data and safety monitoring board that was not affiliated with the study sponsor or the investigators reviewed all data periodically to identify potential safety issues (all complications, including death, stent thrombosis, and myocardial infarction) and to review the conduct of the study (the pace of enrollment, patients' eligibility, and compliance with data collection). The monitoring board did not perform an interim analysis with regard to the pri-

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mary efficacy end point at nine months, since enrollment was completed before the nine-month primary end point was reached in the first patient.

Coronary angiograms, obtained at base line, at the completion of the stenting procedure, and at 240 days of follow-up, were submitted to the angiographic core laboratory (Brigham and Women's Angiographic Core Laboratory, Boston) and were analyzed with the use of a computer-based system (Medis). "Binary" restenosis was defined as stenosis of more than 50 percent of the luminal diameter in the target lesion. Late luminal loss was defined as the difference between the minimal luminal diameter at the completion of the stenting procedure and that measured during follow-up. Quantitative angiographic measurements of the target lesion were obtained in the "in-stent" zone (including only the stented segment) and in the "in-segment" zone (including the stented segment as well as the margins 5 mm proximal and distal to the stent).

Intravascular ultrasonographic examinations were performed after the index stenting procedure and at 240 days in a subgroup of 250 consecutive patients at 17 centers. With the use of intravascular ultrasonography, qualitative assessments and quantitative determinations of the areas and volumes of the vessels, stents, and lumens were made by the intravascular ultrasonography core laboratory (Cardiovascular Core Analysis Laboratory, Stanford University, Stanford, Calif.).

STUDY END POINTS

The primary end point of this study was failure of the target vessel, defined as the occurrence of any of the following within 270 days after the index procedure: death from cardiac causes, Q-wave or non–Q-wave myocardial infarction, or revascularization of the target vessel (emergency or elective coronary-artery bypass grafting [CABG] or repeated percutaneous transluminal coronary angioplasty [PTCA]).

The secondary clinical end points included death from any cause, revascularization of the target lesion (clinically driven CABG or repeated PTCA due to restenosis or closure of the target lesion), and stent thrombosis. All major adverse events were determined for the in-hospital period, for the out-of-hospital period, and cumulatively for the 270 days after the placement of the stent.

STATISTICAL ANALYSIS

The planned sample size of 1100 patients provided 80 percent statistical power to detect a 40 percent reduction in the rate of the primary end point at 270 days (from 15 percent with the standard stent to 9 percent with the sirolimus-eluting stent) with a 5 percent false positive rate (two-sided). We prespecified that the effectiveness analysis and the safety evaluation were to be based on data from all patients who underwent randomization except those who were withdrawn before they received the assigned treatment (as described below). The differences between the treatment groups were evaluated with the use of analysis of variance or with Wilcoxon rank-sum scores for the continuous variables, when appropriate. The Cochran–Mantel–Haenszel statistic, with control for the clinical center, was used for the analysis of categorical variables. The rate of survival free of target-vessel failure during the 270-day follow-up period was analyzed with the use of the

Table 1. **Characteristics of the Patients and the Lesions.***

Characteristic	All Patients (N=1058)	Sirolimus-Stent Group (N=533)	Standard-Stent Group (N=525)
Age (yr)	62.3±11.1	62.1±11.2	62.4±11.0
Male sex (%)	71	73	70
Diabetes mellitus (%)	26	25	28
Hyperlipidemia (%)†	74	73	75
Hypertension (%)	68	68	68
Current smoker (%)	20	18	22
Previous myocardial infarction (%)	31	28	33
Angina pectoris (%)			
Exertional angina	58	59	59
Angina while at rest	23	23	23
Unstable angina‡	53	53	54
Target artery (%)			
Left anterior descending coronary artery	44	44	43
Right coronary artery	31	30	32
Left circumflex coronary artery	25	25	24
Multivessel disease (%)	42	41	42
ACC–AHA class (%)			
A	8	7	8
B1	36	34	38
B2	33	33	34
C	23	26	21
Diameter of reference vessel (mm)	2.80±0.47	2.79±0.45	2.81±0.49
Length of lesion (mm)	14.4±5.8	14.4±5.8	14.4±5.8

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups. ACC denotes American College of Cardiology, and AHA American Heart Association.

† Hyperlipidemia was defined as a low-density lipoprotein cholesterol level above 130 mg per deciliter (3.4 mmol per liter).

‡ Unstable angina was defined according to the Braunwald classification.

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actuarial life-table method, and the difference between survival curves was assessed with the log-rank test. To identify factors that might be related to angiographic restenosis and revascularization of the target lesion, logistic-regression models were used. All statistical analyses were performed with the use of SAS software (version 6.12, SAS Institute), and all reported P values are two-sided.

RESULTS

CHARACTERISTICS OF THE PATIENTS AND THE LESIONS

Between February 2001 and August 2001, 1101 patients gave written informed consent and were randomly assigned to one of the two treatment groups. After randomization, 43 patients (4 percent of all patients, 23 in the sirolimus-stent group and 20 in the standard-stent group) were withdrawn from the study and did not receive the assigned treatment. The reasons for withdrawal were the unavailability of the assigned type of stent at the center (in the cases of 4 patients) and the discovery of criteria for exclusion that became apparent only after pretreatment angiography (in 39 patients). The final patient cohort included 1058 patients — 533 in the sirolimus-stent group and 525 in the standard-stent group.

The groups were well matched, with no significant differences in the frequency of cardiac risk factors (Table 1). Among all patients, the mean age was 62 years; 71 percent were men, 31 percent had had a previous myocardial infarction, and 26 percent had diabetes. Cardiac symptoms included exertional angina in 58 percent of patients, angina while at rest in 23 percent, and unstable angina (Braunwald class I, II, or III) in 53 percent. The majority (56 percent) of treated lesions were class B2 or C according to the American College of Cardiology–American Heart Association classification, the average reference-vessel diameter was 2.80 mm, and the mean lesion length was 14.4 mm.

PROCEDURAL FACTORS

There were no differences between the groups in the rate of use of conventional interventions; glycoprotein IIb/IIIa inhibitors were given to 60 percent of patients, the maximal balloon-inflation pressure after stenting was 15 atm, and the mean (±SD) ratio of the stent length to the lesion length was 1.6±0.6. An average of 1.4 stents were implanted per target lesion, with overlapping stents in 28 percent of patients.

QUANTITATIVE CORONARY ANGIOGRAPHY

The dimensions of the lesion at base line were similar in the two groups (Table 2). Follow-up angiographic data were available for 350 patients in the sirolimus-stent group (86 percent of the patients assigned to undergo angiographic follow-up) and 353 in the standard-stent group (85 percent of the patients assigned to undergo angiographic follow-up). Table 2 shows that at follow-up, the minimal luminal diameter, stenosis as a percentage of the lu-

Table 2. **Results of Quantitative Coronary Angiography.***

Variable	In-Stent Zone			In-Segment Zone		
	Sirolimus Stent	Standard Stent	P Value	Sirolimus Stent	Standard Stent	P Value
Minimal luminal diameter (mm)						
Before procedure	0.98±0.40	0.97±0.38	0.68	0.99±0.40	0.97±0.38	0.68
After procedure	2.67±0.40	2.68±0.42	0.98	2.38±0.45	2.40±0.46	0.63
At 240 days	2.50±0.58	1.69±0.79	<0.001	2.15±0.61	1.60±0.72	<0.001
Stenosis (% of luminal diameter)						
Before procedure	65.1±12.6	65.6±12.1	0.46	65.1±12.6	65.6±12.1	0.46
After procedure	5.4±8.2	6.0±7.9	0.22	16.1±9.7	16.2±8.5	0.80
At 240 days	10.4±16.5	40.1±25.3	<0.001	23.6±16.4	43.2±22.4	<0.001
Late luminal loss (mm)†	0.17±0.45	1.00±0.70	<0.001	0.24±0.47	0.81±0.67	<0.001
Restenosis (% of patients)‡	3.2	35.4	<0.001	8.9	36.3	<0.001

* Plus–minus values are means ±SD.

† Late luminal loss was defined as the difference between the minimal luminal diameter immediately after the placement of the stent and the minimal luminal diameter at 240 days. The data are for the 701 patients for whom both postprocedural and follow-up measurements of the minimal luminal diameter were available.

‡ Restenosis was defined as stenosis of 50 percent of the luminal diameter on the 240-day follow-up angiogram.

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minal diameter, and the late luminal loss in both the in-stent zone and the in-segment zone were all improved with the sirolimus stent as compared with the standard stent (P<0.001 for all comparisons). The frequency of binary in-stent restenosis (stenosis of at least 50 percent of the luminal diameter) was 3.2 percent in the sirolimus-stent group and 35.4 percent in the standard-stent group (P<0.001), and the frequency of in-segment restenosis was 8.9 percent in the sirolimus-stent group and 36.3 percent in the standard-stent group (P<0.001). The higher rate of in-segment restenosis in the sirolimus-stent group was due to a smaller reduction in late luminal loss in the in-segment zone than in the in-stent zone and a higher rate of restenosis at the proximal margin of the stent than at the distal margin or in the body of the stent.

INTRAVASCULAR ULTRASONOGRAPHY

The use of sirolimus-eluting stents, as compared with the use of standard stents, resulted in reductions in the neointimal volume in the in-stent zone (4.4 mm^3 vs. 57.6 mm^3, P<0.001) and in the in-stent obstruction as a percentage of volume (3.1 percent vs. 33.4 percent, P<0.001).

CLINICAL OUTCOMES

Major adverse cardiac events are listed in Table 3. In-hospital events occurred at a similar frequency in the two groups (including death, myocardial infarction, and repeated revascularization); the proportion of patients with any in-hospital major adverse event was 2.4 percent in the sirolimus-stent group and 1.5 percent in the standard-stent group (P=0.38). There was a lower rate of out-of-hospital adverse events during the 270 days of follow-up in the sirolimus-stent group than in the standard-stent group; reductions included those in the number of patients with non–Q-wave myocardial infarction (from 7 to 1, P=0.04), the number requiring revascularization of the target lesion (from 87 to 21, P<0.001), and the number with any major adverse event (from 93 to 26, P<0.001). Similarly, the number of patients reaching the primary clinical end point, failure of the target vessel within 270 days, was reduced by 58 percent with sirolimus stents (from 110 to 46, P<0.001). The rate of survival free of target-vessel failure for 270 days increased from 78.6 percent with a standard stent to 91.1 percent with a sirolimus stent (P<0.001) (Fig. 1).

Stent thrombosis was infrequent, and the rate was similar in the two treatment groups. There were no acute stent thromboses (occurring less than 24 hours after placement of the stent), there was one case of subacute stent thrombosis (occurring between 1 and 30 days after placement) in each group, and there were four late stent thromboses (occurring between 31 and 270 days after placement) — one in the sirolimus-stent group and three in the standard-stent group. The cumulative frequency of stent

Table 3. Major Adverse Cardiac Events in the Hospital and outside of the Hospital during 270 Days of Follow-up.*

Variable	Sirolimus-Stent Group (N=533)	Standard-Stent Group (N=525)	P Value
	no. of patients (%)		
In-hospital events			
Death	1 (0.2)	0	
Myocardial infarction	12 (2.3)	8 (1.5)	
Q-wave	2 (0.4)	0	
Non–Q-wave	10 (1.9)	8 (1.5)	
Target-lesion revascularization	1 (0.2)	0	
CABG	0	0	
PTCA	1 (0.2)	0	
Any major adverse cardiac event	13 (2.4)	8 (1.5)	
Out-of-hospital events			
Death	4 (0.8)	3 (0.6)	
Myocardial infarction	3 (0.6)	9 (1.7)	
Q-wave	2 (0.4)	2 (0.4)	
Non–Q-wave	1 (0.2)	7 (1.3)	0.04
Target-lesion revascularization	21 (3.9)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	19 (3.6)	83 (15.8)	<0.001
Any major adverse cardiac event	26 (4.9)	93 (17.7)	<0.001
Cumulative to 270 days			
Death	5 (0.9)	3 (0.6)	
Myocardial infarction	15 (2.8)	17 (3.2)	
Q-wave	4 (0.8)	2 (0.4)	
Non–Q-wave	11 (2.1)	15 (2.9)	
Target-lesion revascularization	22 (4.1)	87 (16.6)	<0.001
CABG	3 (0.6)	8 (1.5)	
PTCA	20 (3.8)	83 (15.8)	<0.001
Any major adverse cardiac event	38 (7.1)	99 (18.9)	<0.001
Target-vessel failure	46 (8.6)	110 (21.0)	<0.001
Stent thrombosis	2 (0.4)	4 (0.8)	

* P values are given only for significant differences. The total numbers of patients who underwent target-lesion revascularization may not equal the number who underwent coronary-artery bypass grafting (CABG) plus the number who underwent percutaneous transluminal coronary angioplasty (PTCA), because some patients underwent both procedures; the numbers given for any major adverse cardiac event in the cumulative analysis do not equal the numbers given for in-hospital events plus out-of-hospital events, because some patients had more than one event.

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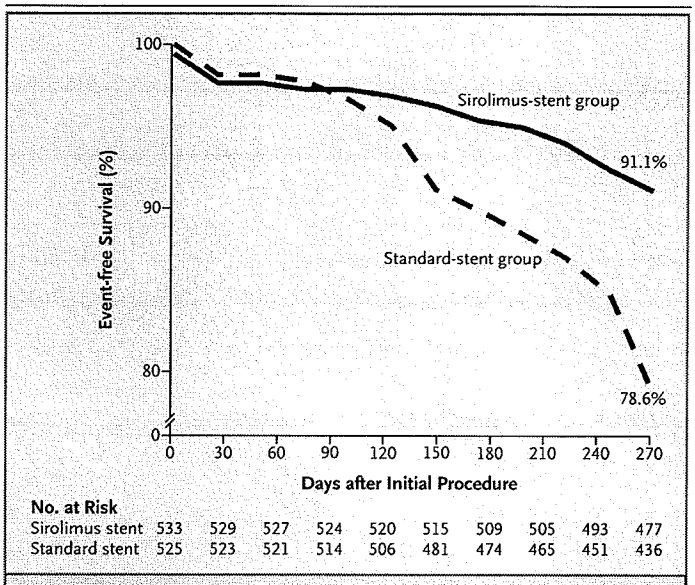

Figure 1. **Actuarial Rate of Survival Free from Target-Vessel Failure among Patients Who Received Either a Sirolimus-Eluting Stent or a Standard Stent.**
The rate of event-free survival was significantly higher in the sirolimus-stent group than in the standard-stent group (P<0.001 by the Wilcoxon and log-rank tests).

thrombosis was 0.4 percent in the sirolimus-stent group and 0.8 percent in the standard-stent group.

SUBGROUP ANALYSES, MULTIVARIABLE ANALYSES, AND ASSESSMENTS OF TREATMENT EFFECTS

Among the 279 patients with diabetes (26 percent of the total study population; 131 patients in the sirolimus-stent group and 148 in the standard-stent group), the absolute frequency of in-segment restenosis and the absolute frequency of target-lesion revascularization were higher than those among patients without diabetes in both treatment groups, but the relative reductions after the placement of a sirolimus stent were of similar magnitude (the rate of in-segment restenosis was reduced from 50.5 percent to 17.6 percent, P<0.001; and the rate of target-lesion revascularization was reduced from 22.3 percent to 6.9 percent, P<0.001).

Among the third of the patient population with the smallest vessels (averaging 2.32 mm in diameter in the sirolimus-stent group and 2.29 mm in the standard-stent group), there was less (albeit still significant) improvement with sirolimus stents in both the rate of in-segment restenosis (18.4 percent, vs. 42.9 percent in the standard-stent group; P<0.001) and the rate of target-lesion revascularization (7.3 percent vs. 20.6 percent, P<0.001). Among the patients with the smallest vessels who received sirolimus stents, the restenosis was usually located at the proximal margin of the stent.

In addition to reducing the overall frequency of angiographic restenosis, the use of sirolimus stents altered the patterns of post-stenting restenosis. The mean length of a restenotic lesion was 9.1±5.8 mm after the placement of a sirolimus stent, as compared with 14.8±7.4 mm after the placement of a standard stent (P<0.001), with a diffuse pattern (a lesion length of more than 10 mm) in 58 percent of cases after the placement of a standard stent, as compared with only 13 percent of cases after the placement of a sirolimus stent (P<0.001).

The association of known risk factors for restenosis with the treatment effect of the sirolimus stent on either angiographic or clinical restenosis was evaluated with the use of multivariable logistic-regression modeling of the rate of in-segment restenosis within 240 days and the rate of target-lesion revascularization within 270 days. In the model of in-segment restenosis, diabetes was significantly associated with an increased risk of restenosis (odds ratio, 2.39; P<0.001), as were the diameter of the reference vessel (odds ratio per 1-mm decrement, 0.54; P=0.001) and the length of the lesion (odds ratio per 1-mm increment, 1.02; P=0.01).

Similarly, in the model of target-lesion revascularization, diabetes was significantly associated with an increased risk of restenosis (odds ratio, 1.65; P=0.03), as were the diameter of the reference vessel (odds ratio per 1-mm decrement, 0.37; P<0.001) and the length of the lesion (odds ratio per 1-mm increment, 1.05; P<0.001). According to both of these models, assignment to the sirolimus-stent group was associated with a significant reduction in the risk of restenosis (odds ratio for in-segment restenosis, 0.24; odds ratio for target-lesion revascularization, 0.17; P<0.001 for both comparisons).

Figure 2 shows the consistent beneficial effect of sirolimus-eluting stents on the risk of target-lesion revascularization in important clinical and angiographic subgroups, including those defined according to sex, the presence or absence of diabetes, whether or not the lesion was located in the left anterior descending artery, the size of the vessel, the length of the lesion, and the presence or absence of overlapping stents.

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Variable	No. of Patients	Rate of Target-Lesion Revascularization (%)	
		Sirolimus stent	Standard stent
Overall	1058	4.1	16.6
Male sex	753	4.4	16.6
Female sex	305	3.4	16.5
Diabetes			
Yes	279	6.9	22.3
No	779	3.2	14.3
Left anterior descending coronary artery			
Yes	462	5.1	19.8
No	596	3.4	14.3
Vessel diameter			
Small <2.75 mm	522	6.3	18.7
Large ≥2.75 mm	523	1.9	14.8
Lesion length			
≤13.5 mm	519	3.2	16.1
>13.5 mm	519	5.2	17.4
Overlapping stents			
Yes	344	4.5	17.7
No	714	3.9	16.1

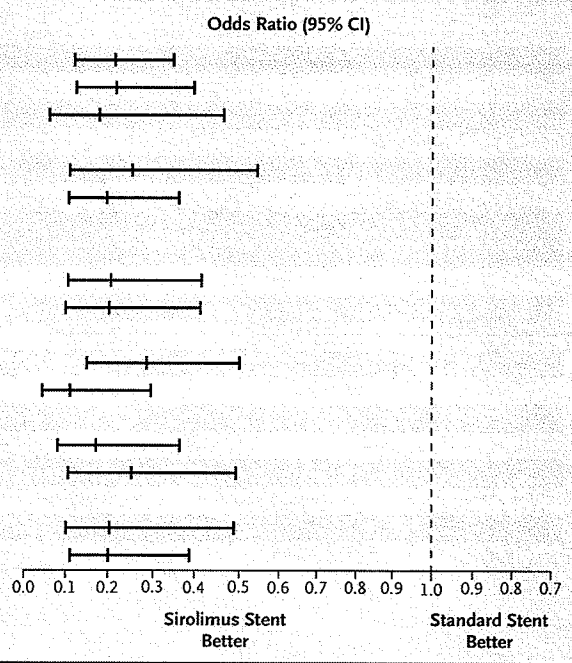

Figure 2. Rates of Target-Lesion Revascularization (Either Percutaneous Transluminal Coronary Angiography or Coronary-Artery Bypass Grafting) and Odds Ratios at 270 Days for Various Subgroups of Patients.

For the analyses in terms of vessel diameter and lesion length, the variable was dichotomized at the median value. P<0.001 for all comparisons between groups. CI denotes confidence interval.

DISCUSSION

In comparison with previous studies of sirolimus-eluting stents,[23-25] our trial enrolled patients with more challenging conditions, including a higher frequency of cardiac risk factors (especially diabetes), more complex lesion morphology, and longer lesions. Nevertheless, the suppression of in-stent neointimal hyperplasia was again demonstrated after the placement of sirolimus-eluting stents, both on angiography (an 83 percent reduction in late luminal loss and a 91 percent reduction in the rate of in-stent restenosis) and on intravascular ultrasonography (a 92 percent reduction in neointimal volume). Moreover, the clinical manifestations of excessive neointimal hyperplasia were similarly improved, with a 77 percent reduction in the rate of out-of-hospital target-lesion revascularization and an 85 percent reduction in the rate of out-of-hospital non–Q-wave myocardial infarction. There were no untoward angiographic complications (e.g., late aneurysms), and the rates of adverse clinical events (including stent thromboses) were not significantly higher in the sirolimus-stent group than in the standard-stent group.

The subgroup analyses indicated that after the placement of a sirolimus stent, the exposed margins of stents that did not cover the entire region of balloon injury were the primary sites of restenosis, which occurred predominantly at the proximal stent margin in smaller vessels. Thus, we would recommend the use of a technique including predilation with shorter balloons, the use of longer single stents in order to cover the entire zone of balloon injury, and dilation after stenting (as needed) with short, high-pressure balloons within the stented regions.

In addition to the reduction in the frequency of restenosis, the pattern of post-stenting restenosis

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differed with sirolimus-eluting stents: whereas restenotic lesions in standard stents were diffuse, those in sirolimus-eluting stents were focal.[26] Such focal post-stenting lesions may typically be treated successfully with the use of simple balloon angioplasty,[27,28] minimizing the need for subsequent vascular brachytherapy.[29,30] Both patients with diabetes and those with lesions in smaller vessels have higher absolute rates of restenosis, although the relative reduction in the rate of restenosis is preserved. Most important, the sirolimus-eluting stent was found to have a consistent treatment effect in analyses of a broad range of subgroups of patients and lesions.

To determine the ultimate clinical usefulness of sirolimus-eluting stents, additional clinical trials are required that involve patients with disease in a bifurcation, chronic total occlusions, saphenous-vein graft disease, restenosis after stenting, failure of vascular brachytherapy, lesions in the left main coronary artery, and multivessel disease. The findings in two-year follow-up examinations in a cohort of 45 patients who were treated with sirolimus-eluting stents are encouraging, indicating that the angiographic and clinical efficacy are maintained.[31] However, the long-term safety and durability of this very potent site-specific therapy require further substantiation in larger cohorts of patients.

A clinically efficacious drug-eluting stent system requires a meticulous integration of the stent design, drug-carrier vehicle, and therapeutic agent. Preliminary stent-based results with paclitaxel, a well-described chemotherapeutic agent that suppresses microtubule dynamics,[32-34] delivered through a polymer-matrix formulation, have also shown promise.[35] The results of our clinical trial demonstrate that the sirolimus-eluting stent has achieved the delicate balance of preserved safety and improved efficacy and thus has the potential to alter the course of coronary therapy in the future.

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Dr. Moses reports having received consulting fees from Cordis (Johnson & Johnson) and lecture fees from Johnson & Johnson and holding equity interests in Johnson & Johnson; Dr. Leon reports having received consulting and lecture fees from and holding equity interests in Cordis; Dr. Popma reports having received consulting fees, lecture fees, and grant support from Cordis; Dr. Fitzgerald reports having received consulting fees, lecture fees, and grant support from Cordis; Dr. Kereiakes reports having received honorariums and research grants from Johnson & Johnson (Centocor); Dr. Williams reports having received consulting fees and grant support from Cordis; and Dr. Teirstein reports having received consulting and lecture fees from and holding equity interests in Cordis, and having received royalties from Cordis related to the sale of radiation-delivery catheters.

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APPENDIX

The following investigators and institutions participated in the multicenter, randomized, double-blind study of the sirolimus-eluting balloon-expandable stent in the treatment of patients with de novo native coronary-artery lesions (the SIRIUS trial): Sponsor — Cordis, Warren, N.J., D. Donohoe (medical director), J. Jaeger (program director), E. Keim, L. Lonzetta, L. Reynolds, J. Batiller, C. Hill; Data and Safety Monitoring Board — B. Gersch (chair), Rochester, Minn.; M. Farkouh, New York; R. Bonow, Chicago; R. D'Agostino (biostatistician), Boston; G. Mintz, Washington, D.C.; A. Schwartz, New York; Data Management — Harvard Clinical Research Institute, Boston; *Coordination* — E. Catapane; *Clinical Events Committee* — D. Cohen (chair), L. Epstein, J. Kannam, W. Manning, J. Markis; Electrocardiography Core Laboratory — P. Zimetbaum, M. Josephson; Core Angiographic Laboratory — Brigham and Women's Hospital, Boston, J. Popma (director); Core Intravascular Ultrasound Laboratory — Stanford University Medical Center, Stanford, Calif., P. Fitzgerald (director); Clinical Sites — J. Carrozza, P. Rooney, Beth Israel Deaconess Medical Center, Boston; S. Ellis, A. Robakowski, Cleveland Clinic Foundation, Cleveland; J. Douglas, P. Hyde, Emory University Hospital, Atlanta; J. Moses, M. Leon, V. Laroche, Lenox Hill Hospital, New York; P. Teirstein, E. Anderson, Scripps Clinic, La Jolla, Calif.; E. Perin, M. Harlan, Texas Heart Institute, Houston; R. Wilensky, M. Walsh, Hospital of the University of Pennsylvania, Philadelphia; L. Satler, J. Lavoie, Washington Hospital Center, Washington, D.C.; M. Cleman, C. Roberts, Yale University Hospital, New Haven, Conn.; S. DeMaio, L. Rogers, Baylor Medical Center, Dallas; E. Fry, A. Taylor, M. Potrikus, Saint Vincent's Hospital, Indianapolis; A. Yeung, C. McWard, Stanford University Medical Center, Stanford, Calif.; J. Zidar, S. Dickerson, Duke University Medical Center, Durham, N.C.; W. O'Neill, K. Dimick, William Beaumont Hospital, Royal Oak, Mich.; G. Mishkel, J. Daniels, P. Sullivan, Saint John's Hospital, Springfield, Ill.; D. McCormick, L. Mark, B. Connor, Hahnemann Hospital, Philadelphia; D. Roberts, B. Seiler, Sutter Memorial General Hospital, Sacramento, Calif.; D. Holmes, D. Shelstad, Saint Mary's Hospital, Rochester, Minn.; F. Kiernan, D. Murphy, Hartford Hospital, Hartford, Conn.; M. Midei, E. Yaker, Saint Joseph's Hospital, Baltimore; D. Williams, J. Muratori, T. Chaffee, Rhode Island Hospital, Providence; T. Fischell, S. Baskerville, Borgess Medical Center, Kalamazoo, Mich.; S. Oesterle, I. Palacios, C. Cothern, Massachusetts General Hospital, Boston; S. Yakubov, C. Gilliland, P. Vieira, Riverside Methodist Hospital, Columbus, Ohio; D. Kereiakes, R. Lengerich, Christ Hospital–Lindner Center, Cincinnati; C. Davidson, L. Eckman, Northwestern Memorial Hospital, Chicago; C. Brown, K. Reid, Piedmont Hospital, Atlanta; C. Lambert, T. Watts, N. Parker, Health First Institute, Melbourne, Fla.; D. Baim, R. Monboquette, Brigham and Women's Hospital, Boston; A. Raizner, R. Benfield, Methodist Hospital, Houston; B. Cohen, R. Lao, Morristown Memorial Hospital, Morristown, N.J.; N. Laufer, M. Balfour, Good Samaritan Regional Medical Center, Phoenix, Ariz.; S. Raible, B.J. Henehan, Jewish Hospital Heart and Lung Institute, Louisville, Ky.; P. Coleman, A. Nofi, Northern California Medical Association, Santa Rosa; S. Sorenson, K. Robinson, Latter Day Saints Hospital, Salt Lake City; M. Mooney, P. Demmer, Abbott Northwestern Hospital, Minneapolis; T. Feldman, J. Lopez, L. Loftis, University of Chicago Hospitals, Chicago; J. Lasala, K. Zuchowski, S. Aubuchon, Barnes Jewish Hospital, St. Louis; R. Caputo, C. Lastinger, Saint Joseph's Hospital, Syracuse, N.Y.; C. O'Shaughnessy, T. Julio, L. St. Marie, L. Barr, North Ohio Heart Center, Elyria; H. Madyoon, T. Weaver, Saint Joseph's Medical Center, Stockton, Calif.; J. Midwall, L. Herlan, JFK Memorial Hospital, Atlantis, Fla.; M. Bates, L. Lukhart, Charleston Area Medical Center, Charleston, W.Va.; M. Clark, L. Pennington, Integris Oklahoma Heart Institute, Okla-

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